Clinical Study Synopsis for Public Disclosure

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2. SYNOPSIS

NAME OF COMPANY:	
Galderma R&D	
NAME OF FINISHED MEDICINAL PRODUCT:	***For regulatory use only***
Not applicable	
NAME OF ACTIVE INGREDIENT(S):	
CD5789	
Title of study:	Exploratory study to assess facial tolerability after daily application of several concentrations and formulations containing CD5789 in acne subjects

- Study centers

A total of 6 centers participated in this study: 3 in Hungary, 2 in France, and 1 in Belgium.

- Clinical phase

Phase 2a: therapeutic exploratory

- Study period
  - Date of first subject screened: 4 April 2011
  - Date of last subject completed:27 July 2011

- Study objectives

To evaluate the facial tolerability and subject's adherence to treatment of different formulations of CD5789 when applied once daily (QD) over 4 weeks by acne subjects, in comparison with Tazarotene 0.1%.

- Study design

This was a multicenter, randomized, evaluator-blind, parallel-group exploratory study to investigate the facial tolerability and subject adherence to treatment for different formulations of CD5789 in subjects with acne vulgaris. Tazarotene 0.1% Gel was selected as an active comparator.

Two cohorts were defined. Within each cohort, the corresponding treatments and number of subjects to be allocated to each treatment group were as follows:

- Cohort 1
  - A: CD5789 50 µg/g Cream A, n=14
  - B: CD5789 25 µg/g Cream A, n=14
  - C: CD5789 50µg/g Gel, n=7
  - D: Tazarotene 0.1% Gel, n=7

- Cohort 2
  - E: CD5789 50 µg/g Cream B, n=14
  - C: CD5789 50µg/g Gel, n=7
  - D: Tazarotene 0.1% Gel, n=7

- Total number of subjects

A sample size of 42 evaluable subjects was planned for Cohort 1 and 28 evaluable subjects for Cohort 2, for a total of 70 evaluable subjects. The sample size was an approximation, as no formal hypothesis testing was planned in this study. A total of 68 subjects were randomized.

- Diagnosis and key inclusion and non-inclusion criteria
  - Key inclusion criteria
    - Male or female subjects 18-35 years old;
    - Moderate to severe facial acne vulgaris;
    - At least 20 inflammatory lesions and 30 non-inflammatory lesions;
    - If female of childbearing potential, she agrees to use a highly effective double-barrier contraception method for the duration of the study and one month after the last study drug application.
  - Key exclusion criteria
    - The subject had severe forms of acne requiring systemic treatment (acne conglobata, acne fulminans) or secondary acne form (chloracne, drug-induced acne, etc.);
    - The subject had a known allergy or sensitivity to any of the components of the study drugs

- Test Product Dosage Form

	Investigational Product	Investigational Product	Investigational Product	Investigational Product	Comparator Product
Name of active ingredient/ concentration	CD5789 25 µg/g (0.0025%)	CD5789 50 µg/g (0.0050%)	CD5789 50 µg/g (0.0050%)	CD5789 50 µg/g (0.0050%)	Tazarotene 0.1%
Internal code (if applicable)	code 0219.0889 Cream A	code 0219.0890 Cream A	code 0219.0108 Gel	code 0219.0102 Cream B	N/A
Pharmaceutical Form	Cream	Cream	Gel	Cream	Gel
Packaging (type and size)	30 mL amber glass bottle with Bakelite cap				15 g aluminium tube
Storage Conditions	Store below 25°C ; Do not freeze, Do not refrigerate		Store below 25°C Do not freeze	Store below 25°C Do not freeze, Do not refrigerate	Store below 30°C
Dose regimen					
Route	Topical				
Frequency	Once daily in the evening				
Duration of administration	29 days				
Location of treated area	Face				

- Efficacy assessment
  - Lesion counts: inflammatory (papules, pustules), non-inflammatory (open and closed comedones), other acne lesion count (nodules); total lesion count was calculated as the sum of inflammatory lesions, non-inflammatory lesions, and nodules;
  - Efficacy criteria
    - Not applicable, as this study was not designed to show the efficacy of CD5789. However, lesion count data were obtained (total, inflammatory, and non-inflammatory) to prepare data summaries on the numbers of lesions and also the percent reductions in lesions over time by treatment group.

- Other assessment
  - Cosmetic acceptability questionnaire
  - Facial photographs (at a pre-selected center)

- Safety assessment
  - Adverse events
  - Physical examinations and vital signs
  - Laboratory safety testing
  - Local tolerance

- Principal statistical methods

No inferential analyses were conducted for this study.

Subject disposition, demographics, baseline characteristics, previous therapies, and concomitant therapies were summarized by treatment group using descriptive statistics.

Efficacy data were analyzed at each visit for the Safety Population. Lesion counts (inflammatory, non-inflammatory and total) as well as changes and percent reduction in lesion counts from baseline were descriptively summarized by visit and by treatment.

Adverse events, general physical examination, vital signs, laboratory parameters and cosmetic acceptability questionnaires were summarized by descriptive statistics.

Local tolerability assessments were summarized by treatment using means over time, frequency by severity over time, and worst response (from Day 1 to Day 29) over time.

- Sample size

For Cohort 1, screening of 50 subjects was planned in order to enroll 42 evaluable subjects.

For Cohort 2, screening of 33 subjects was planned in order to enroll 28 evaluable subjects, with allocation to treatment groups as follows: 7 subjects in the CD5789 Gel and Tazarotene 0.1% Gel groups and 14 subjects in the CD5789 50 µg/g Cream B group in order to have the same numbers of subjects in the corresponding groups across the 2 cohorts.

No formal hypothesis testing was planned in this study.

- Results
  - Demographics and baseline disease characteristics
    - For randomized subjects, no apparent imbalances in demographic characteristics were observed among the treatment groups (Table 1). All (100%) of randomized subjects were Caucasian, and the randomized subjects were predominantly males (57.4%). The mean age of randomized subjects overall was 21.6 years, ranging from 18 to 33 years.
    - Subjects were required to have at least 20 inflammatory lesions and 30 non-inflammatory lesions on the face to be eligible for this study. In each treatment group, mean non-inflammatory lesion counts were higher than mean inflammatory lesion counts (Table 2). No obvious differences were observed among the treatment groups for any lesion count category.

Table 1 Demographic characteristics, Safety Population

	SCREENED	RANDOMIZED					
	Total	CD5789 50µg/g CREAM B	CD5789 25µg/g CREAM A	CD5789 50µg/g CREAM A	CD5789 50µg/g GEL	TAZAROTENE 0.1% GEL	Total
Age (years)							
n	70	12	14	16	12	14	68
Mean	21.6	20.8	21.6	21.4	22.9	21.4	21.6
Median	21.0	19.0	20.5	21.0	21.5	20.0	21.0
SD	3.6	2.9	4.3	2.8	4.4	3.7	3.6
(Min,Max)	(18,33)	(18,26)	(18,31)	(18,27)	(18,33)	(18,31)	(18,33)
Race (n, %)							
Caucasian	69 (98.6%)	12 (100.0%)	14 (100.0%)	16 (100.0%)	12 (100.0%)	14 (100.0%)	68 (100.0%)
Hispanic	1 (1.4%)	0	0	0	0	0	0
Total	70 (100.0%)	12 (100.0%)	14 (100.0%)	16 (100.0%)	12 (100.0%)	14 (100.0%)	68 (100.0%)
Sex (n, %)							
Female	31 (44.3%)	4 (33.3%)	5 (35.7%)	8 (50.0%)	5 (41.7%)	7 (50.0%)	29 (42.6%)
Male	39 (55.7%)	8 (66.7%)	9 (64.3%)	8 (50.0%)	7 (58.3%)	7 (50.0%)	39 (57.4%)
Total	70 (100.0%)	12 (100.0%)	14 (100.0%)	16 (100.0%)	12 (100.0%)	14 (100.0%)	68 (100.0%)

In this study, the Safety Population included all randomized subjects
Max=maximum; Min=Minimum; SD=standard deviation
Data source: Table 14.2.1.2

Table 2 Baseline disease characteristics, Safety Population

	CD5789 50µg/g CREAM B	CD5789 25µg/g CREAM A	CD5789 50µg/g CREAM A	CD5789 50µg/g GEL	TAZAROTENE 0.1% GEL
Total lesion counts					
n	12	14	16	12	14
Mean	63.2	67.1	65.3	62.2	67.1
SD	6.0	11.9	15.1	8.5	10.1
Median	62.5	66.0	60.0	60.5	64.5
(Min,Max)	(53.0,72.0)	(53.0,90.0)	(55.0,111.0)	(53.0,78.0)	(51.0,90.0)
Inflammatory lesion counts					
n	12	14	16	12	14
Mean	25.8	23.6	25.7	25.3	28.6
SD	4.5	2.8	4.9	5.6	7.4
Median	24.5	22.0	25.0	23.0	27.0
(Min,Max)	(21.0,37.0)	(20.0,29.0)	(20.0,40.0)	(21.0,40.0)	(21.0,50.0)
Non-inflammatory lesion counts					
n	12	14	16	12	14
Mean	37.3	43.1	39.6	36.7	38.4
SD	3.9	10.7	14.7	4.4	7.5
Median	36.5	39.5	34.5	36.5	37.5
(Min,Max)	(31.0,45.0)	(31.0,67.0)	(31.0,91.0)	(31.0,46.0)	(30.0,62.0)

Max=maximum; Min=Minimum; SD=standard deviation
Data source: Table 14.2.2.1

- Efficacy
  - For total lesions, at the end of the 4-week treatment period, the mean numbers of total lesions were lower than Day 1 in all treatment groups, ranging from 21.0 lesions in the CD5789 50 µg/g Cream B group to 28.9 lesions in the CD5789 50 µg/g Cream A group (Table 3). Total lesions on Day 29 were reduced in all treatment groups relative to baseline, ranging from 55.4% in the CD5789 50 µg/g Cream A group to 68.2% in the CD5789 50 µg/g Gel group (Table 4). The largest early effect was observed in the CD5789 50 µg/g Cream B group, for which a 40.6% mean percent reduction in total lesions was observed at Day 8.
  - For inflammatory lesions, mean numbers of lesions on Day 29 were lower than Day 1 in all treatment groups, ranging from 8.4 lesions in the CD5789 50 µg/g Gel group to 13.1 lesions in the CD5789 50 µg/g Cream A group. Inflammatory lesions on Day 29 were reduced in all treatment groups, ranging from 51.0% in the CD5789 50 µg/g Cream A group to 66.2% in the CD5789 50 µg/g Gel group. In general, a cumulative effect was observed over the treatment period in each treatment group with respect to mean percent reduction in inflammatory lesions.

- For non-inflammatory lesions, mean numbers of lesions were lower than Day 1 in all treatment groups, ranging from 10.5 lesions in the CD5789 50 µg/g Cream B group to 16.2 lesions in the CD5789 25 µg/g Cream A group. Non-inflammatory lesions on Day 29 were reduced in all treatment groups, ranging from 58.7% in the CD5789 50 µg/g Cream A group to 71.5% in the CD5789 50 µg/g Cream B group. A cumulative effect was observed over the treatment period in each treatment group with respect to mean percent reduction in non-inflammatory lesions.

Table 3 Total lesion counts, Safety Population

		CD5789 50µg/g CREAM B	CD5789 25µg/g CREAM A	CD5789 50µg/g CREAM A	CD5789 50µg/g GEL	TAZAROTENE 0.1% GEL
Day 01	n	12	14	16	12	14
	Mean	63.2	67.1	65.3	62.2	67.1
	SD	6.0	11.9	15.1	8.5	10.1
	Median	62.5	66.0	60.0	60.5	64.5
	(Min,Max)	(53.0,72.0)	(53.0,90.0)	(55.0,111.0)	(53.0,78.0)	(51.0,90.0)
Day 08	n	11	14	16	12	14
	Mean	37.5	46.9	50.8	40.6	48.4
	SD	12.0	9.3	21.4	17.3	14.5
	Median	35.0	47.5	44.0	36.5	43.5
	(Min,Max)	(25.0,64.0)	(35.0,64.0)	(28.0,108.0)	(18.0,70.0)	(28.0,73.0)
Day 29	n	11	13	16	12	14
	Mean	21.0	25.2	28.9	20.2	23.2
	SD	15.9	12.6	13.0	13.2	11.9
	Median	15.0	24.0	28.5	18.5	22.5
	(Min,Max)	(3.0,54.0)	(13.0,47.0)	(5.0,53.0)	(4.0,52.0)	(5.0,46.0)
Day 35	n	11	13	16	12	13
	Mean	22.3	25.3	26.9	20.3	21.7
	SD	17.8	13.2	11.7	12.2	9.6
	Median	19.0	25.0	27.5	20.0	19.0
	(Min,Max)	(3.0,59.0)	(7.0,53.0)	(5.0,52.0)	(3.0,44.0)	(8.0,44.0)

Max=maximum; Min=Minimum; SD=standard deviation
Data source: Table 14.2.3.1

Table 4 Percent reduction in total lesion counts from Day 1, Safety Population

		CD5789 50µg/g CREAM B	CD5789 25µg/g CREAM A	CD5789 50µg/g CREAM A	CD5789 50µg/g GEL	TAZAROTENE 0.1% GEL
Day 08	n	11	14	16	12	14
	Mean	40.6	28.2	23.9	35.9	26.5
	SD	18.6	18.6	19.8	21.8	23.1
	Median	45.0	31.1	28.7	37.3	24.5
	(Min,Max)	(0.0,63.9)	(0.0,53.2)	(-20.0,49.1)	(1.4,66.0)	(-11.9,63.1)
Day 29	n	11	13	16	12	14
	Mean	66.1	61.3	55.4	68.2	65.5
	SD	27.4	20.7	19.1	18.1	16.8
	Median	79.2	67.9	56.6	68.4	66.6
	(Min,Max)	(5.3,95.0)	(32.8,85.6)	(23.2,91.5)	(26.8,93.9)	(30.0,91.7)
Day 35	n	11	13	16	12	13
	Mean	63.9	60.8	58.3	67.8	67.5
	SD	31.1	22.6	17.6	17.4	13.2
	Median	72.2	61.8	56.7	66.9	68.6
	(Min,Max)	(-3.5,95.0)	(10.2,89.9)	(24.6,91.5)	(38.0,95.5)	(41.7,86.7)

Max=maximum; Min=Minimum; SD=standard deviation
Data source: Table 14.2.3.1

- Other assessments (cosmetic acceptability)
  - For the characteristics of color, smell, and texture, a majority of subjects in each treatment group had neutral or favorable responses. In addition, most subjects in each treatment group responded that they strongly agreed that the study drug was easy to apply and all subjects in each treatment group either strongly or somewhat agreed that the formulation rubbed in easily.

- Safety
  - A total of 34 AEs were reported for 17 subjects (Table 5). The overall incidence of AEs did not appear to increase with dose, as the numbers of subjects with AEs in the CD5789 50 µg/g groups (Cream A, Cream B, and Gel) was not notably higher than in the CD5789 25 µg/g Cream A group. However, the CD5789 25 µg/g Cream A group was the only treatment group in which no dermatologic AEs were reported. Likewise, no apparent dose-dependent trends were observed for individual AEs.
  - The most common AE overall was headache, which was reported in 5 subjects: 1 subject each in the CD5789 50 µg/g Cream B, CD5789 25 µg/g Cream A, and CD5789 50 µg/g Cream A groups, and 2 subjects in the Tazarotene 0.1% Gel group. The only severe AE in this study was reported in the CD5789 50 µg/g Cream B group: an SAE of facial palsy reported for Subject 5715-031, which was assessed by the Investigator as not related to the study drug.

- All AEs that were assessed by the Investigators as related to study drug were in the skin and subcutaneous tissue disorders System Organ Class (Table 6). Dry skin and skin irritation were the most common related AEs overall, reported for 3 subjects each overall. No related AEs were reported in the CD5789 25 µg/g Cream A group. No more than 1 subject in any treatment group reported any particular related AE.
- All AEs that were assessed as related to study drug were of mild or moderate severity. The largest number of moderate AEs was reported in the Tazarotene 0.1% Gel group (3 subjects) and included skin burning sensation, skin irritation, herpes zoster, and increased blood bilirubin in 1 subject each.
- No deaths occurred in this study. An unrelated SAE of facial palsy was reported for 1 subject in the CD5789 50 µg/g Cream B group, and resulted in the subject's discontinuation from the study.
- No AESIs were observed in this study.
- Local tolerance for CD5789 50µg/g Cream B appeared to be slightly better relative to CD5789 50µg/g Gel and Tazarotene 0.1% Gel for the moderate and severe parameters in the erythema and stinging/burning categories (Figure 1). However, mean scores over time did not always reflect this for all local tolerability parameters. Furthermore, CD5789 50µg/g Cream B did not appear to be highly dissimilar from CD5789 50µg/g Gel when comparing mean scores over time. The mean scores in the CD5789 treatment groups peaked after 1 week of treatment, followed by a progressive diminishing over time that was more rapid for stinging/burning.
- No clinically meaningful abnormal trends were observed in laboratory parameters, vital signs, or physical examinations for any treatment groups.

Table 5 Overview of adverse events, Safety Population

	CD5789 50µg/g CREAM B		CD5789 25µg/g CREAM A		CD5789 50µg/g CREAM A		CD5789 50µg/g GEL		TAZAROTENE 0.1% GEL		Total	
	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]
All AEs	8	4 (33.3)	3	3 (21.4)	6	3 (18.8)	5	3 (25.0)	12	4 (28.6)	34	17 (25.0)
Related AEs	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	4	3 (21.4)	13	8 (11.8)
All dermatologic[b] AEs	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	5	3 (21.4)	14	8 (11.8)
Related dermatologic[b] AEs	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	4	3 (21.4)	13	8 (11.8)
Severe AEs	1	1 (8.3)	0	0	0	0	0	0	0	0	1	1 (1.5)
Severe related AEs	0	0	0	0	0	0	0	0	0	0	0	0
AEs of special interest	0	0	0	0	0	0	0	0	0	0	0	0
All SAEs	1	1 (8.3)	0	0	0	0	0	0	0	0	1	1 (1.5)
Related SAEs	0	0	0	0	0	0	0	0	0	0	0	0
All AEs leading to discontinuation	1	1 (8.3)	0	0	0	0	0	0	0	0	1	1 (1.5)
Related AEs leading to discontinuation	0	0	0	0	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0	0	0

Adverse events are defined as events that occurred on the day of, or after, the first use of study drug.

[a] n=Number of subjects with at least one event.

[b] Dermatologic AEs = All AEs related to System Organ Class = Skin and Subcutaneous Disorders.

Data source: Table 14.3.3.1

Table 6 Frequency of related adverse events by System Organ Class and Preferred Term, Safety Population

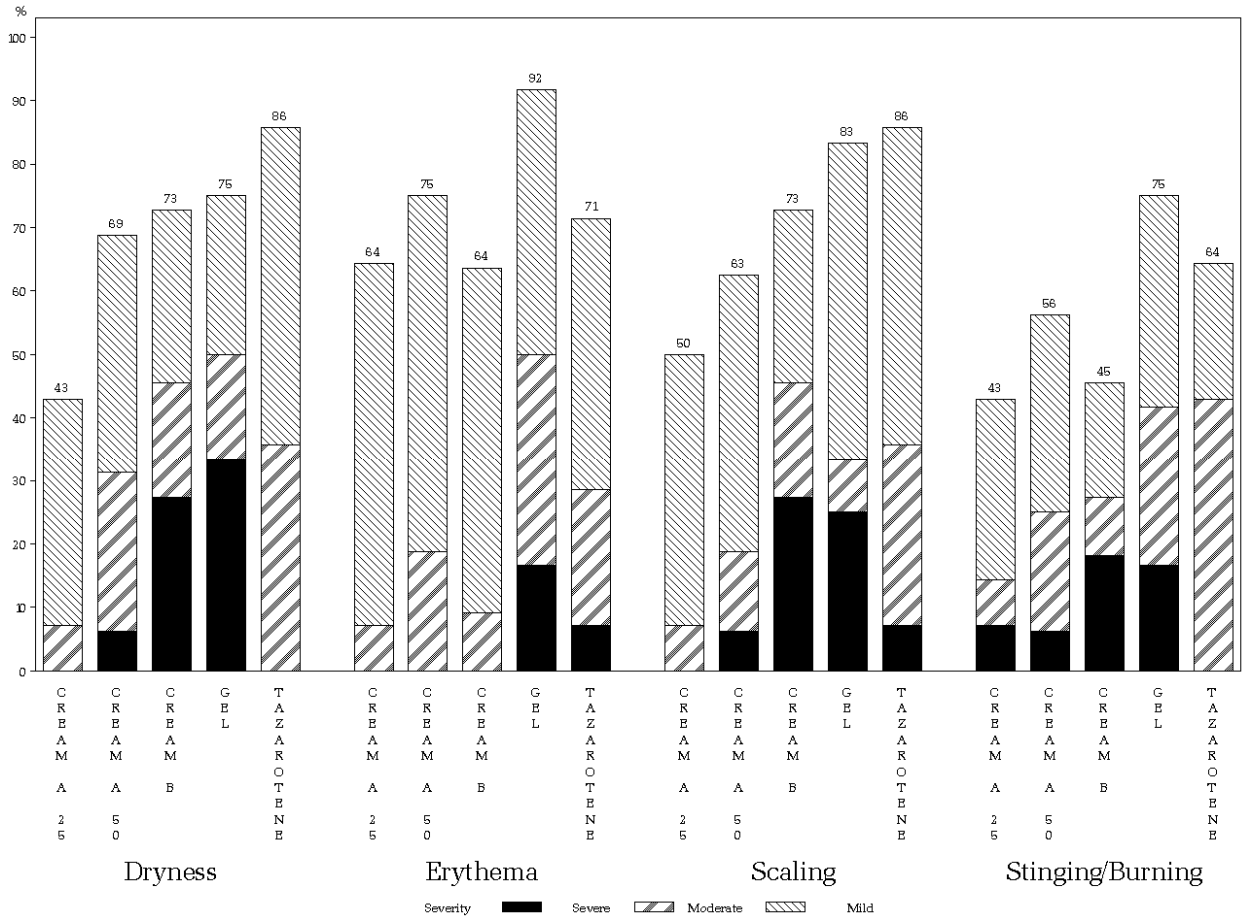
System Organ Class/ Preferred Term	CD5789 50µg/g CREAM B		CD5789 25µg/g CREAM A		CD5789 50µg/g CREAM A		CD5789 50µg/g GEL		TAZAROTENE 0.1% GEL		Total	
	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]
Skin and Subcutaneous Tissue Disorders	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	4	3 (21.4)	13	8 (11.8)
Dry skin	1	1 (8.3)	0	0	0	0	1	1 (8.3)	1	1 (7.1)	3	3 (4.4)
Skin irritation	0	0	0	0	1	1 (6.3)	1	1 (8.3)	1	1 (7.1)	3	3 (4.4)
Pain of skin	1	1 (8.3)	0	0	0	0	0	0	1	1 (7.1)	2	2 (2.9)
Skin burning sensation	1	1 (8.3)	0	0	1	1 (6.3)	0	0	0	0	2	2 (2.9)
Skin exfoliation	0	0	0	0	1	1 (6.3)	0	0	1	1 (7.1)	2	2 (2.9)
Pruritus	1	1 (8.3)	0	0	0	0	0	0	0	0	1	1 (1.5)
Total	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	4	3 (21.4)	13	8 (11.8)

Adverse events are defined as events that occurred on the day of, or after, the first use of study drug.

[a] n=Number of subjects with at least one event.

Data source: Table 14.3.3.5

Figure 1 Incidence of worst score for each sign/symptom, Safety Population



Data source: Figure 5

- Conclusions

For local tolerability (erythema, dryness, scaling, and stinging/burning), mean scores in the CD5789 treatment groups peaked after 1 week of treatment, followed by a progressive diminishing over time, as seen with other topical retinoids. This reduction in local tolerability symptoms was more rapid for stinging/burning.

A noticeable reduction of both inflammatory and non-inflammatory lesions was observed with all CD5789 products tested in this study.

All evaluated concentrations of CD5789 products were well-tolerated and safe. No clinically meaningful abnormal trends were observed in laboratory parameters, vital signs, or physical examinations for any treatment groups for the duration of the study.